Biclustering Algorithms for Gene Expression Analysis

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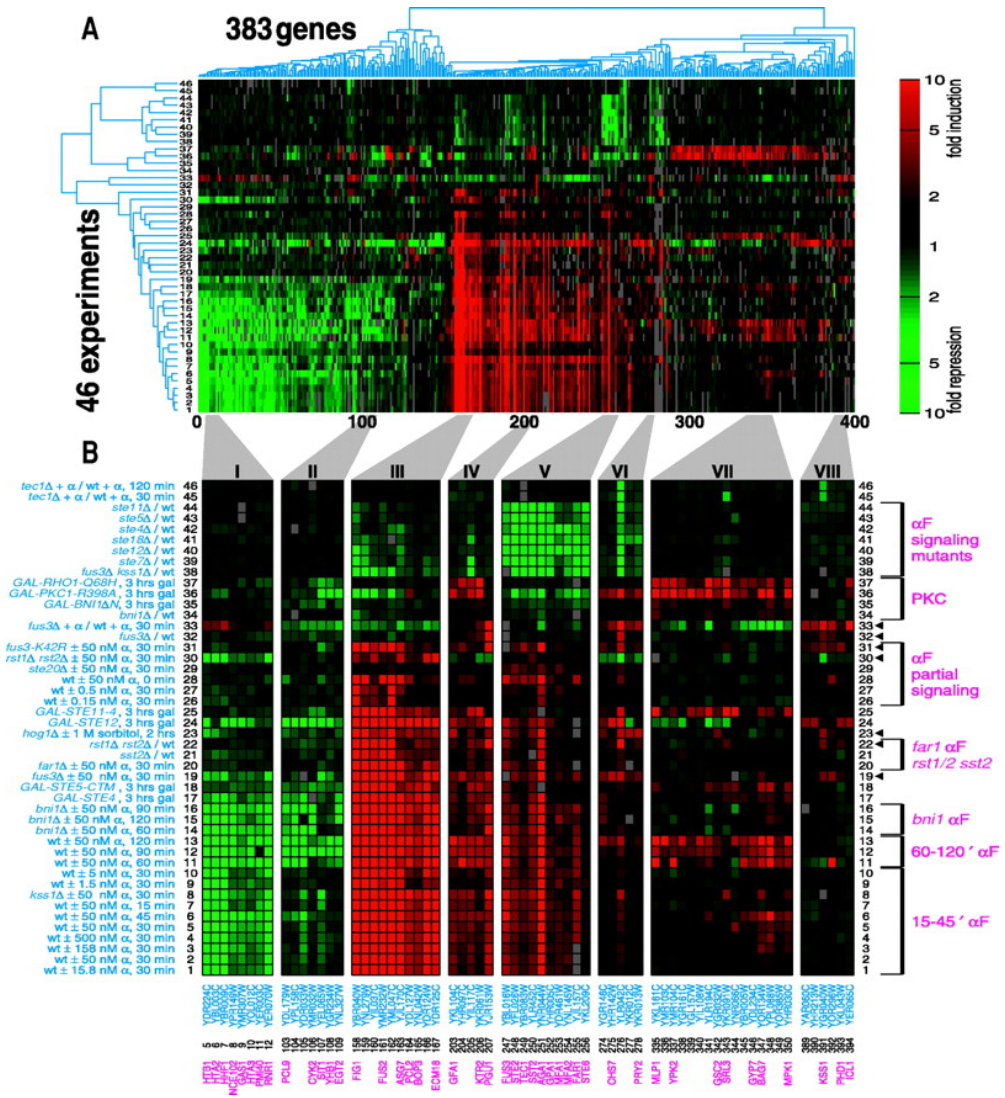
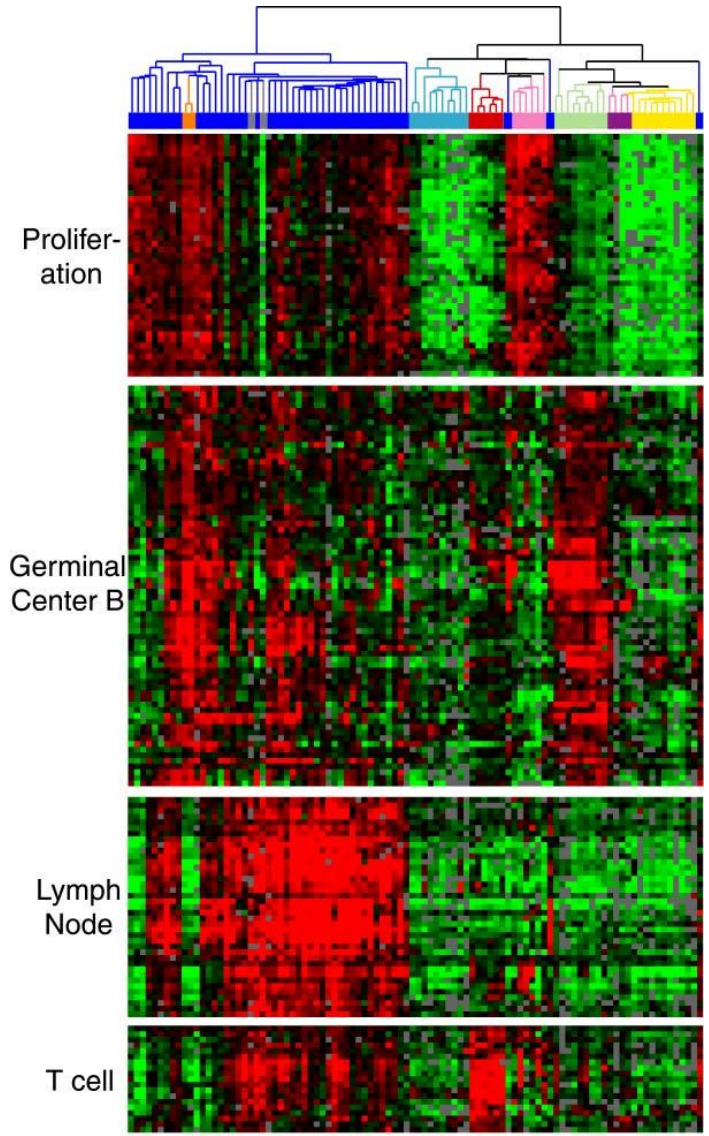
- Considers *all* genes to be equally important for all samples.
- What if only a subset of the genes are co-expressed across only a subset of the samples?
- What if different subsets of the genes are co-expressed for different subsets of samples?

Example: Roberts et al. (Science 2000)



Example: Alizadeh et al. (Nature 2000)



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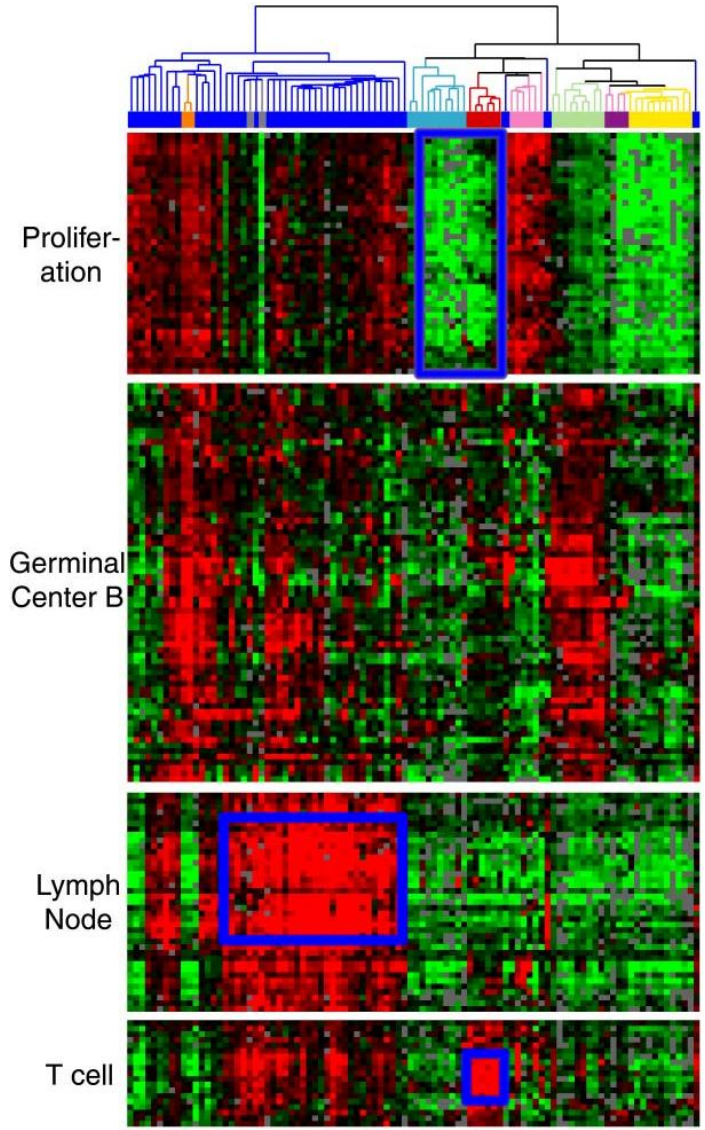

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- A *bicluster* is a subset of genes and a subset of samples with the property that the selected genes are co-expressed only in the selected samples.
- By selecting samples *and* genes, a bicluster represents condition-specific patterns of expression.
- Issues in biclustering:
  - How do we measure the degree of co-expression of a subset of genes in a subset of samples?
  - How many biclusters should we compute?
  - How do we compare two different sets of biclusters?

History of Biclustering

- Block clustering: Hartigan 1972, recursively partition matrix into blocks.
- Biclustering formulated in the context of gene expression data by Cheng and Church, ISMB 2000.
- Since 2000, a number of papers have been published on biclustering.
  - Finding statistically-significant biclustering: Sharon, Tanay, and Shamir, ISMB 2002.
  - Iterative signature algorithm: Bergmann, Ihmels, and Barkai, Phys Review E 2003
  - Two surveys of biclustering:
    - Madeira and Oliveira, IEEE/ACM Transactions on Computational Biology and Bioinformatics, 2004.
    - Tanay, Sharan, and Shamir, Handbook of Computational Molecular Biology, 2006.

Biclustering: Cheng and Church

- Defined the score of a bicluster to be its mean squared residue.
- Developed an iterative algorithm for computing biclusters with residue less than δ (specified by the user) by addition and deletion of genes and samples.
- To find multiple biclusters, they "erase" the values in the previously-computed biclusters and continue.

Mean Squared Residue

- A = matrix of gene expression values, a_{ij} = value in the ith row and jth column of A.
- I = subset of genes/rows, J = subset of conditions/columns.
- A_{IJ} = submatrix of A containing the rows in I and the columns in J.
- The mean squared residue of A_{IJ} is

$$H_{IJ} = \frac{1}{|I||J|} \sum_{i \in I, j \in J} (a_{ij} - a_{iJ} - a_{Ij} - a_{IJ})^2 \text{, where}$$

- a_{iJ} = average of values in A_{IJ} along row i, a_{Ij} = average of values in A_{IJ} along column j and a_{IJ} = average of all values in A_{IJ}.

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- Constant matrix: 0.
- Single element: 0.
- Matrix with elements chosen randomly from the interval $[a, b]$ has expected mean squared residue $(b - a)^2/12$.

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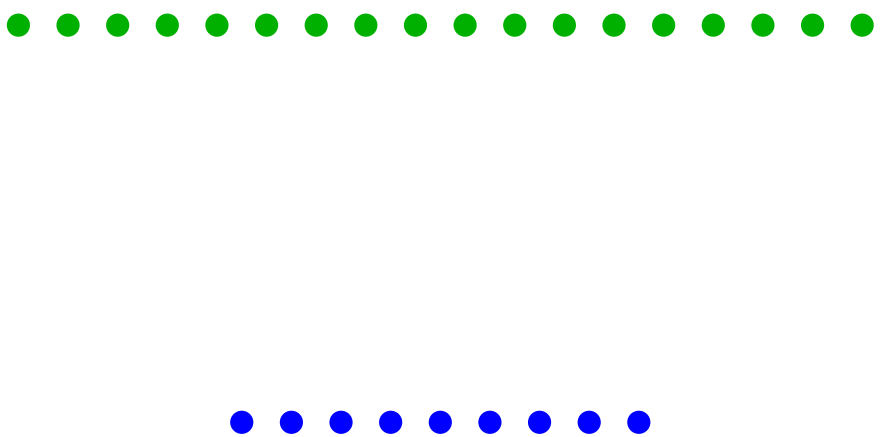
  - Square: maximise $|I| = |J|$, NP-Hard .
  - Area: maximise $|I||J|$, also NP-Hard (proven after the Cheng and Church paper).

Algorithms

- Since the problems are computationally intractable, use heuristics to find biclusters of "large" size.
- Basic idea: add/delete a row/column until mean squared residue does not decrease.
  - Delete a row/column if its deletion improves mean squared residue.
  - Add a row/column if its addition improves mean squared residue.
  - Add some tricks to allow deletion/addition of multiple rows/columns so that it is not necessary to recompute mean squared residue after each change.

Biclustering: Sharan, Tanay, and Shamir

- Graph model: each gene is a node, each sample is a node.



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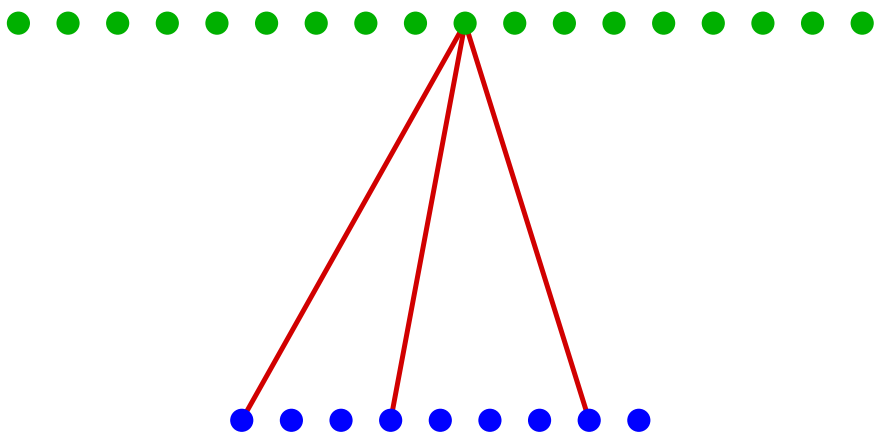

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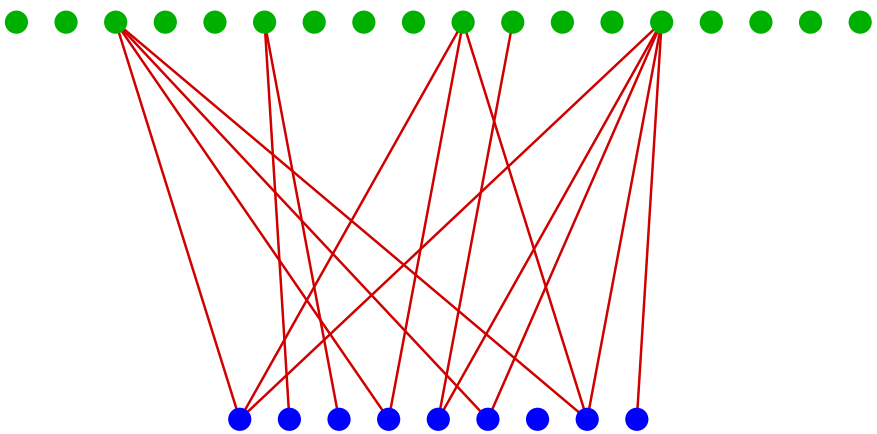

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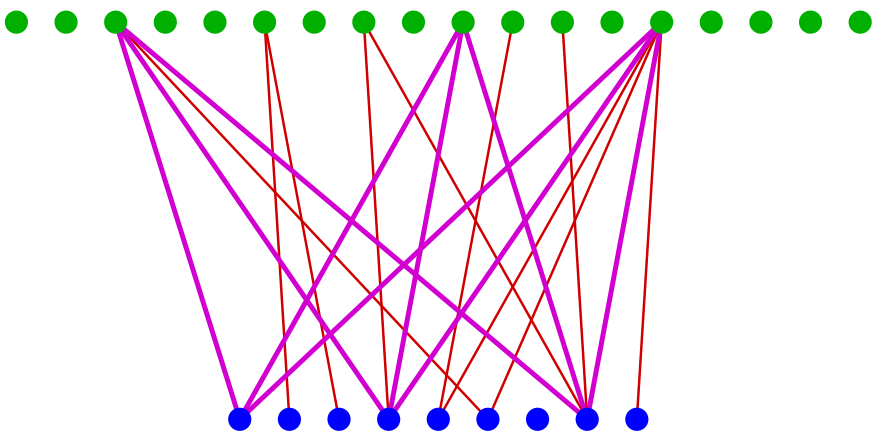
- Bicluster $\equiv$ clique; weight of a bicluster is the sum of the weights of its edges.



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- Add some heuristics: iteratively add/delete node that improves the weight the most until no modification is possible.

Assessing Edge Weights

- Goal: assess statistical significance of a bicluster in "random" data; assign edge weights so that weight of a bicluster is equal to its statistical signficance.
- U = set of genes, V = set of conditions, E is the set of edges.
- Simple model: assume each edge occurs with probability $p = |E|/(|U||V|)$.
- Given a bicluster $H = (U', V', E')$, the probability $p(H)$ of observing a bicluster at least as dense as H is the probability that if we select each of the $|U'||V'|$ possible edges with probability p, we will select E' or more edges:

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$$\sum_{|E'| \leq i \leq |U'||V'|} \binom{|U'||V'|}{i} p^i (1-p)^{|U'||V'|-i}.$$

Assessing Edge Weights Continued

- $p(H) = \sum_{|E'| \leq i \leq |U'||V'|} \binom{|U'||V'|}{i} p^i (1-p)^{|U'||V'|-i}$.
- If $p \leq 1/2$, $p(H) \leq 2^{|U'||V'|} p^{|E'|} (1-p)^{|U'||V'|-|E'|}$.
- To minimise $p(H)$, maximise $-\log p(H) = -|U'||V'| - |E'| \log p - (|U'||V'| - |E'|) \log(1-p)$.
- Assign each edge in the graph a positive weight $-1 - \log p$ and each edge not in the graph a negative weight $-1 - \log(1-p)$.